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PATENT

REMARKS

Upon entry of the amendment, claims 13-16, 20, 42-53, and 60-83 are pend ng in the application. Claims 66-83 are newly added. Support for new claims 66 and '3 can be found in the specification on p. 1, lines 7-9; p. 10, line 8; p. 11, lines 8-16; p 12, line 8; p. 13, lines 21-22 and 28-31; p. 14, line 12 through p. 15, line 8; and in origir al claims 21 and 22. Support for new claims 67 and 74 can be found in original claim 20. Support for new claims 68-70 and 75-77 can be found in the specification on p. 12, lines 11-15. Support for claims new claims 71, 72, 78, and 79 can be found in the specification on p. 14, lines 32-35. Support for new claim 80 can be found in the specification on p. 13, lines 15-17. Support for claim 81 can be found in the specification on p. 14, lines 26-29. Support for claim 82 can be found in the specification on p. 14, lines 32-35. Support for claim 83 can be found in the specification on p. 14, lines 32-35 and p. 15, lines 4-6.

I. Claim Objections

Claims 21 and 22 have been rewritten as independent claims 66 (incorporat ng the requirements of dependent claim 21 into independent claim 60) and claim 73 (incorporating the requirements of dependent claim 22 and intervening dependent claim 14 into independent claim 60).

II. 35 U.S.C. 112, First Paragraph – Written Description

Reconsideration is requested of the rejection of claims 13-16, 20, 42-47, an l 60-65 under 35 U.S.C. §112, first paragraph, on the asserted basis that the claims co ntain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors were in possession of the claimed invention at the time the application was filed.

A. The Legal Standard

"Compliance with the written description requirement is essentially a fact-ba sed inquiry that will 'necessarily vary depending on the nature of the invention claimed. "

Amgen Inc., v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1330 (Fed. Cir 2003) (*citing*, Enzo *Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002)). The standard is whether the description allows persons of ordinary skill in the art to recognize that the inventor had possession of the claimed invention at the time of filing, "even if every nuance of the claims is not explicitly described in the specification." *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996); *see also*, *Vas-Cath*, 935 F.2d 1555, 1557 (Fed. Cir. 1991). An applicant may demonstrate possession of a claimed invention by describing ***distinguishing identifying characteristics*** sufficient to demonstrate that applicant was in possession of the claimed invention. MPEP §2163 (citing *Regents of the University of California v. Eli Lilly*, 119 F. 3d 1559, 1568 (1998))(emphasis added). The PTO has the initial burden of demonstrating why a person of ordinary skill in the art would not recognize in the disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 264 (C.C.P.A. 1976).

In this instance, the Office not only failed to apply the correct legal standard, it misinterpreted applicant's specification.

B. Written Description Support in the Specification

1. Applicant's Specification

Applicants' specification lists numerous dyes that could be used in the claimed reagents, exemplifying a representative number of species in a commercially preferred embodiment described in Example 1. In addition, applicants' specification contains *in haec verba* support for the language contained in the generic claims. Based upon this disclosure, especially in light of the high degree of knowledge in the art, discussed in detail below, one of ordinary skill would have understood that applicants were in possession of the invention as generically claimed.

2. Applicant's Example 1

According to the Office "[o]f the 180 dyes evaluated, but 6 were found suitable."[1] This interpretation of applicant's data is simply incorrect. As explained in Example 1, "Figure 6 summarizes the selection process. From 180+ red dyes (absorbance max between 450 and 570 nm) (Table 1) approximately 40 anionic dyes were selected (Table 2)."[2] Contrary to the Office's interpretation, therefore, 180 dyes were not evaluated; only the 40 identified in Table 2 were evaluated.

The 40 dyes appearing in Table 2 were first evaluated for color. As recited in the specification, the color red was selected for ***aesthetic reasons only*** and ***confers no particular advantage*** as a tracer dye.[3] Of the 40 dyes appearing in Table 2, approximately half[4] of the dyes were eliminated from further consideration **not** because they would not work with a thermostable DNA polymerase, but simply because applicants chose to demonstrate a particular ***commercially preferred*** embodiment wherein the tracer dye was a certain shade of red that is commonly associated in the field with the assignee Sigma-Aldrich Company. From this, a person of ordinary skill could not have logically concluded that any of the eliminated dyes were unsuitable for use in the invention; rather, the person of ordinary skill could only have concluded that the inventor preferred a different shade of red.

The remaining 20 dyes listed in Table 2 were further and successively evaluated in (i) ethanol precipitation,[5] (ii) "Qiagen" solid phase extraction[6] and (iii) PCR-toxicity

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[1] Office action (mailed 08/11/2004) at p. 6.

[2] Specification at page 18, lines 27-30.

[3] Specification, p. 18, lines 19-20.

[4] Seventeen of the dyes were eliminated because of color. An additional 3 were eliminated because they lacked sufficient solubility. *See*, specification, p. 26, lines 1-4.

[5] Specification, p. 25, lines 5-13.

[6] Specification, p. 25, lines13-19.

tests.[7] These three tests were performed in order of the least to most laborious[8] with only those performing satisfactorily being subjected to the next test. Significantly, the first two of these tests, *i.e.*, the ethanol precipitation and "Qiagen" tests, merely demonstrate suitability for a down-stream commercial application of the product of a PCR reaction carried out using a composition of the present invention; stated another way, satisfactory performance in these tests is not probative of the suitability of these dyes as a tracer reagent in PCR. The third test, *i.e.*, the PCR toxicity test, demonstrates whether the preferred dyes would be suitable for use as a tracer reagent. Because of the methodology selected, only 11 dyes were subjected to the PCR toxicity test and, of these, 5 were found suitable.

In summary, only 40 dyes were evaluated. Of these, 20 were eliminated because of color (17) or solubility (3) considerations. Of the remaining 20 dyes, 9 were eliminated because of unsatisfactory performance in an ethanol precipitation test (5) or Qiagen (4) test, leaving 11 for evaluation in the only test which is meaningful for determining suitability of the dyes for use in the invention as claimed. Of these 11, 5 performed suitably.

3. Skill and Knowledge in the Art

According to the Office, "it appears that applicant is attempting to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, through obviousness."[9] The Office, however, appears to have misunderstood the thrust of applicants' position; armed with (1) the broad and enabling description which appears in applicants' specification and corresponds to the language of the claims, and (2) the exemplification of applicants' invention in Example 1 in which five different dyes were shown, a person of ordinary skill would have understood that applicants were in possession of the invention generically claimed.

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[7] Specification, p. 26, line 22 through p. 27, line 19.

[8] Specification, p. 18, lines 19-21.

[9] Office action (mailed 08/11/2004) at page 6.

In this instance, applicants were not arguing that the invention would have been obvious, but rather that once applicants described their invention generically and exemplified it with several dyes, a person of ordinary skill would have understood that applicants were in possession of the invention as claimed. This analysis is consistent with Office's Guidelines for examination:

> The written description requirement for a claimed genus may be satisfied **through sufficient description of a representative number of species by actual reduction to practice . . . or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus** . . . See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.
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> A **"representative number of species"** means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. **The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."** See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004) [quotation omitted] "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004) [quotation omitted]. On the other hand, **there may be situations where one species adequately supports a genus.** *See, e.g., Rasmussen*, 650 F.2d at 1214, 211 USPQ at 32627 [quotation omitted]; *In re Herschler*, 591 F.2d 693, 697, 200 USPQ 711, 714 (CCPA 1979) (disclosure of corticosteroid in DMSO sufficient to support claims drawn to a method of using a mixture of a "physiologically active steroid" and DMSO because **"use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description."**);

> *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 285 (CCPA 1973) (the phrase "air or other gas which is inert to the liquid" was sufficient to support a claim to "inert fluid media" **because the description of the properties and functions** of the air or other gas segmentizing medium **would suggest to a person skilled in the art that appellant's invention includes** the use of "inert fluid" broadly.). However, in *Tronzo v. Biomet*, 156 F.3d at 1159, 47 USPQ2d at1833 (Fed. Cir. 1998), the disclosure of a species in the parent application did not suffice to provide written description support for the genus in the child application. **What constitutes a "representative number" is an inverse function of the skill and knowledge in the art.** Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. . . For example, in the molecular biology arts, if an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acids encoding a given amino acid sequence, but not necessarily any particular species. Cf. In re Bell, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993) and *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 U.S.C. 112, para. 1.[10]

Therefore, what constitutes a representative number of species sufficient to support a claim to a genus encompassing the species is an inverse function of the skill and knowledge in the art – that is to say, the greater the skill and knowledge in the art, the fewer species that must be disclosed by an applicant in order to support a claim to a genus. In this particular instance, the degree of skill and knowledge in the art regarding the existence of polymerase-compatible dyes is quite high, and therefore, applicants' disclosure in Example 1 would convey to one of ordinary skill that applicants were in possession of reagents comprising more than just the dyes disclosed therein.

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[10] MPEP 2163, emphasis added.

This high degree of skill and knowledge is demonstrated by the Ward declaration[11] and the art cited during the course of the examination of this application. For example, Hoppe et al.,[12] cited in the specification,[13] note the following:

> Two dyes that we have found to be compatible with PCR are also shown in [Figure 1]. Tartrazine (FD&C yellow #5) (Aldrich Chemical, Milwaukee, WI) inhibited the reaction at approximately 1500 mg/ml. Yellow food coloring from the supermarket (Schilling brand, McCormick and Co., Baltimore, MD) is also PCR-compatible, up to a dilution in the final reaction of approximately 1:160. This food coloring consists primarily of yellow #5 with a small amount of red dye that separates out on electrophoresis. We could not add enough cresol red (Aldrich Chemical) to inhibit the formation of PCR products because of its limited solubility.

Similarly, Setterquist et al.[14] disclose an agarose encapsulated PCR reagent, the contents of which are disclosed in Table 1.[15] The components of the reagent include the dye cresol red.

Even more compelling is Nardone et al.[16] Nardone et al. disclose compositions comprising nucleotide phosphoramidite precursors covalently coupled to a quencher

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[11] Declaration of Brian Ward, dated July 29, 2002, and submitted with applicants' Amendment B on July 29, 2002. This declaration states that the dyes used in the particular embodiments of the invention are representative of numerous dyes that can be used with similar success. *See*, Ward Declaration, ¶¶ 20 and 27.

[12] Hoppe et al., *BioTechniques* 12:679-680 (1992).

[13] Specification, p. 3, line 29 through p. 4, line 5, wherein it is noted that dyes such as cresol red, tartrazine, and yellow food coloring # 5 were compatible with the thermostable DNA polymerase Taq.

[14] *Nucl. Acids. Res.*, 24(8): 1580-1581 (1996). This reference is cited in the IDS submitted July 26, 2004 and discussed in Amendment D submitted May 24, 2004.

[15] Sutterquist et al., p. 1580, second column.

[16] U.S. Patent 6,117,986. This reference was first cited by the Office in an action dated September 11, 2002.

molecule, wherein the quencher molecule can be a number of non-flourescent dyes, including non-fluorescent azo dyes and non-fluorescent triphenyl methyl dyes.

> Examples of non-fluorescent azo dyes which may be used according to the invention are as follows: acid aldzarin violet N, acid black 24, acid blue 29, acid blue 92, acid blue 113, acid blue 120, acid blue 161, acid orange 8, acid orange 51, acid orange 74, acid red 1, acid red 4, acid red 8, acid red 37, acid red 40, acid red 88, acid red 97, acid red 106, acid red 151, acid red 183, acid violet 5, acid violet 7, acid yellow 17, acid yellow 25, acid yellow 29, acid yellow 34, acid yellow 38, acid yellow 40, acid yellow 42, acid yellow 65, acid yellow 76, acid yellow 99, alizarin yellow 66, alizarin blue, black B, palatine chrome black 6BN, mordant black 3, basic red 29, basic blue 66, brilliant yellow chrysophenine, chrysoldin, crocein orange G, crystal scarlet, fast black K salt, fast corinth V salt, fast garnet GBC, fat brown B, fat brown RR, mordant blue 9, mordant brown 1, mordant brown 4, mordant brown 6, mordant brown 24, mordant brown 33, mordant brown 48, mordant orange 1, mordant orange 6, mordant orange 10, oil red E6N, oil red O, orange 11, orange G, palatine chrome black 6BN, palatine fast yellow BLN and topaeolin O. Particularly preferred non-flourescent azo dyes include acid aldzarin violet N, acid black 24, acid blue 92, acid blue 113, acid blue 120, acid orange 8, acid orange 51, acid orange 74, acid red 1, acid red 4, acid red 8, acid red 37, acid red 88, acid red 151, acid red 183, acid yellow 34, acid yellow 40, acid yellow 76, crocein orange G, crystal scarlet, mordant blue 9, mordant brown 1, mordant brown 33, mordant orange 1, mordant orange 6, mordant orange 10, orange 11, orange G, palatine chrome black 6BN, palatine fast yellow BLN and topaeolin O.
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> Examples of non-fluorescent triphenyl methyl dyes which can be used according to the invention are selected from: alkali blue 6B, aniline blue, aurintricarboxylic acid, basic violet 14, basic red 9, brilliant green, bromochlorophenol blue, bromocresol purple, chlorophenol red, m-cresol purple, cresol red, crystal violet, ethyl violet, fast green FCF, guinea green B, malachite green, methyl green, new fuschia, pyrocatechol violet, thymol blue, thymolphthalein, victoria blue B, victoria blue R and victoria pure blue, both as the isocyanate or isothiocyanate derivatives. A preferred non-fluorescent triphenyl methyl dye is malachite green derivatized at the 4 position of the phenyl ring with isothiocyanate. Other non-fluorescent dyes that can be used as a quencher include alizarin blue black B, alizarin red S, alizarin violet 3R, fast blue BB, and fast blue RR.

Hoppe et al., Setterquist et al., and Nardone et al. demonstrate that a person of ordinary skill understood that a wide range of dyes, in general, and non-fluorescent dyes,

in particular, were compatible with polymerases in PCR and analogous reactions. Hoppe et al., Setterquist et al., and Nardone et al., however, did not employ the dye in the manner claimed by applicants. When applicants described their invention generically and successfully exemplified it with several dyes, a person of ordinary skill would have understood that applicants were in possession of the entire genus since, as recited in the MPEP, what constitutes a representative number of samples is inversely related to the level of skill in the art and, in this instance, persons of ordinary skill were ***already well aware*** that a wide range of dyes were compatible with polymerases.

Based upon the disclosure in the application and the skill and knowledge in the art, one of skill would readily recognize that applicants were in possession of the claimed reagents wherein the anionic tracer dye is a color other than those specifically demonstrated in Example 1.

III. 35 U.S.C. 103(a) Obviousness Rejection

Reconsideration is requested of the rejection of claims 13-16, 20-22, and 60-65 under 35 U.S.C. 103(a) as being unpatentable over Köster et al. (U.S. Patent No. 5,928,906) in view of Nardone et al. (U.S. Patent No. 6,117,986).

Claim 60, as amended, is generally directed to an aqueous reagent for use in forming a polymerase reaction mixture comprising a thermostable DNA polymerase, a nucleic acid polymer template, a primer, nucleotides, a detectible anionic tracer dye unbound to primer or nucleotides, and a solute to increase the physical density of the reagent. The reagent comprises the thermostable DNA polymerase, the detectible anionic tracer dye, and the solute but being ***free of the primer and the nucleic acid polymer template***, the reagent having an optical density of about 5 to about 500 at a visible wavelength of maximal tracer absorbance and a physical density of at least about 1.01 gm/cm^3, but less than the density of the solute.